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Editorial

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Insights from Decades of Supplementing Calcium and Vitamin D

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The impact of calcium and vitamin D supplementation on long-term health outcomes, including cancer and cardiovascular disease (CVD), remains a subject of considerable debate [1-4]. Recent findings from a comprehensive long-term follow-up trial conducted by Thomson et al. [5] (2024) have provided new insights into this ongoing discussion. The present study examined the extended effects of calcium and vitamin D supplementation on a range of health outcomes in postmenopausal women through a *post hoc* analysis of long-term postintervention follow-up data from the 7-year randomized Women's Health Initiative Calcium and Vitamin D (CaD) trial. This trial included a diverse group of participants from 40 centers, who were randomly assigned to either the supplementation group or a placebo group at a 1:1 ratio. The intervention involved a random 1:1 allocation to either 1,000 mg of calcium carbonate with 400 IU of vitamin D3 daily or a placebo.

Key findings from this longitudinal investigation included a 7% reduction in cancer mortality among those receiving the supplements, contrasted with 6% increase in CVD mortality during a median follow-up of 22.3 years [5]. The study found discernible impacts on fracture, CVD events, cancer incidence, or all-cause mortality. Subgroup analyses categorized based on prior supplementation status before randomization demonstrated a notable 11% decrease in the risk for overall cancer—including a 31% and 19% decrease in the incidence of colorectal cancer and invasive breast cancer, respectively—in those who had not used supplements before. On the contrary, for individuals who had been supplementing prior to the study, the risk ratios were insignificant for cancer outcomes. However, supplementation had no impact on all-cause mortality, irrespective of participants' supplementation status before the study.

The methodology of the study involved a *post hoc* analysis, which is pivotal for understanding the study's contributions and limitations. *Post hoc* analysis, by its nature, involves examining data after an experiment has concluded, often to find patterns not specified *a priori* [6]. While this can yield insightful observations, the absence of predefined hypotheses inherently increases the likelihood of identifying statistically significant results. This is a critical consideration when interpreting the study's findings, as it may influence the robustness of the conclusions regarding the effects of calcium and vitamin D supplementation on health outcomes, such as cancer and CVD mortality. Furthermore, the study's reliance on self-reported supplement use prior to randomization adds another layer of complexity [5]. Differences in the health behaviors and characteristics of women who reported using supplements before the study could have impacted the outcomes. This necessitates a careful interpretation of the results, as the observed benefits or risks associated with calcium and vitamin D supplementation may be partly due to pre-existing differences among the participants, rather than the supplementation itself.

Nonetheless, the findings of a 7% reduction in cancer mortal-

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ity in the group supplemented with calcium and vitamin D align with existing literature [3,4]. A meta-analysis of randomized controlled trials on vitamin D supplementation reported a significant reduction in overall cancer mortality, particularly in individuals without a history of cancer, who did not use additional vitamin D or calcium supplements [3]. These results are also consistent with an early reanalysis of the Women's Health Initiative, which provided evidence of a lower risk of total invasive cancer among users of calcium and vitamin D [4].

Vitamin D plays a crucial role in regulating cell growth, differentiation, and apoptosis, which are major mechanisms involved in cancer development and progression [7]. Additionally, calcium takes part in intracellular signaling pathways that influence cell proliferation and differentiation, potentially contributing to a protective effect against cancer, especially colorectal cancer [8]. The interaction between calcium and vitamin D may have synergistic effects on immune function and the modulation of inflammation [9], both of which are implicated in carcinogenesis. By improving immune surveillance and reducing chronic inflammation, calcium and vitamin D supplementation could create an environment less conducive to tumor growth and metastasis [10], thereby lowering cancer mortality rates. However, it is important to note that most findings in this field, including the current study, are based on observational studies and randomized controlled trials subject to inherent limitations. Future studies should explore the interplay between these nutrients and specific cancer types to provide more targeted insights into their impact on cancer mortality in diverse populations.

The clinically significant finding of a 6% increase in CVD mortality in the intervention group has raised important considerations regarding management and prevention strategies for cardiovascular health [5]. Studies on the complex relationship between calcium intake and cardiovascular outcomes have revealed that excessive calcium supplementation might contribute to arterial calcification and increased risk of myocardial infarction [11]. As a potential mechanism underlying these effects, elevated calcium levels in the bloodstream may lead to vascular calcification and increased arterial stiffness [12,13]. However, a meta-analysis reported that calcium intake within the tolerable upper intake levels (2,000 to 2,500 mg/day) was not associated with increased CVD risk in the general population [12]. Additionally, evidence indicates that the relationship between calcium intake and CVD risk may follow a U-shaped curve [2,14], highlighting a nonlinear interaction where both inadequate and excessive intake could potentially lead to adverse health outcomes. This complexity underscores the importance of a balanced approach to calcium supplementation [13], especially in populations with already sufficient dietary calcium intake, as in this study's participants [5]. Taken together, the findings from previous studies emphasize the need to cautiously interpret research outcomes related to calcium supplementation, especially in regions with adequate dietary calcium.

In conclusion, this study—underpinned by its longitudinal design and large-scale randomized controlled trial framework—offers invaluable insights into the impacts of calcium and vitamin D supplementation on health outcomes over an extended follow-up period. The depth of data derived from such a substantial cohort underscores the potential benefits and complexities associated with these nutritional interventions. Nonetheless, the inherent limitations of *post hoc* analysis warrant a cautious approach to the interpretation of the study's findings. The interdependent effects of calcium and vitamin D complicate the delineation of their respective contributions to cancer and CVD mortality; thus, the precise mechanisms of action remain to be clarified. Future research should aim to disentangle the distinct effects of calcium and vitamin D on cancer and CVD, thereby elucidating their roles in health and disease during prolonged observation periods.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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